Severe and rapid cardiac toxicity from sunitinib therapy in a patient with metastatic renal cell carcinoma

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A 67-year-old man with a history of left-sided renal cell carcinoma (RCC) status after undergoing a radical nephrectomy presented to the oncology clinic after sustaining a pathologic fracture of the left humerus. Computed tomography revealed a right suprarenal mass with invasion into the inferior vena cava (IVC) and right atrium, confirmed to be poorly differentiated RCC on biopsy. Transthoracic echocardiogram (Figure 1) showed tumor thrombus occluding the IVC lumen; the tumor also extended into the right atrium, measuring 8 cm in circumference. Despite this direct invasion, cardiac function remained normal; there was no evidence of valvular or wall motion abnormalities, and left ventricular ejection fraction (LVEF) was preserved at 67%. Therapy for metastatic RCC was initiated with the tyrosine kinase inhibitor sunitinib at 50 mg daily. Body mass index (BMI) at this time was 24.8. Within 12 days of starting therapy, however, the patient exhibited symptoms of New York Heart Association class IV heart failure and was referred to the emergency department. He was aggressively diuresed, placed on bilevel positive airway pressure, and admitted to the intensive care unit. Echocardiogram revealed severe new-onset left ventricular dysfunction, with an LVEF of 5%-10%. Tumor thrombus was largely unchanged and did not interfere with cardiac function. The patient's symptoms were refractory to medical therapy; he requested comfort measures only and died on hospital day 5.

Discussion

The exact rate of cardiac toxicity induced by sunitinib is unknown but has been documented to be as high as 21%.[1,2] However, this rate may be an underestimate, as careful cardiac monitoring of a series of patients on sunitinib has demonstrated that 33.8% of patients experience a cardiac event (eg, increase in cardiac biomarkers, symptomatic arrhythmia, left ventricular dysfunction, or acute coronary syndrome) with nearly half of the patients with cardiac events being asymptomatic.[3] The most important adverse effect from sunitinib is left ventricular dysfunction, with grade 3/4 heart failure occurring in approximately 12.5% of patients.[4] Risk factors for sunitinib-induced cardiac toxicity include preexisting coronary artery disease, hypertension, and heart failure, as well as a BMI <25.[1,2] Notably, there is no clear relationship between sunitinib dose and cardiac toxicity.[2,5]

To our knowledge, our case documents the most severe reduction of LVEF induced by sunitinib, from 67% to 5%-10%. Furthermore, this is a more rapid decline in cardiac function than what is reported in almost all other documented cases. One case series reported cardiac toxicity from sunitinib after a range of 22-435 days,[1] while another multicenter review found that symptomatic heart failure usually occurred after 2-6 cycles[2] (1 cycle being 4 weeks on the drug and 2 weeks off). Indeed, we noted only 2 cases in which cardiac toxicity occurred more rapidly, both manifesting 4 days after initiation of therapy.[5]

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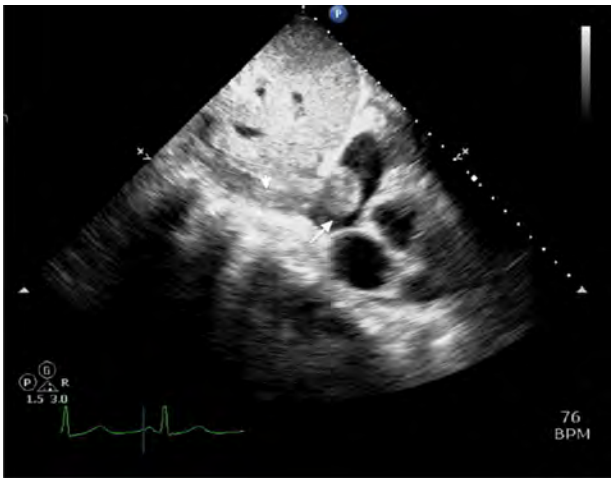

FIGURE 1 Transthoracic echocardiogram (subcostal view) showing occlusive thrombus of the inferior vena cava (arrowhead) with extension into the right atrium (arrow). Tumor in the right atrium measures eight centimeters in circumference. Image provided courtesy of the Division of Cardiology Echocardiography Laboratory at Rhode Island Hospital.

Both of these patients, however, had risk factors for sunitinib-induced cardiac toxicity. One patient had preexisting hypertension, while the other patient had both preexisting coronary artery disease and hypertension, in addition to having been previously treated with bevacizumab (which may also cause cardiac toxicity as an adverse effect[6]). Other than a BMI <25, our patient did not have any such risk factors.

The pathogenesis of cardiac toxicity from tyrosine kinase inhibitors is not fully understood, but tyrosine kinase inhibition affects healthy as well as cancerous cells. A proposed mechanism for cardiac toxicity[7] is the inhibition of ribosomal S6 kinase, which triggers a proapoptotic cascade that results in both myocyte loss and ATP depletion. Exacerbating this process is the inhibition of AMP-activated protein kinase, which would normally conserve ATP by halting ATP-consuming processes, especially in situations of hypoxia. The end result of myocyte loss and ATP depletion is hypertrophy and ventricular dysfunction.

Conclusion

This case illustrates that sunitinib-induced cardiac toxicity, which is a known (but perhaps underestimated) potential adverse effect, can occur rapidly and dramatically, even in patients without risk factors and with previously normal cardiac function. Close cardiac monitoring is essential when this agent is used in the treatment of cancer.

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